Remarks

The undersigned would like to thank Examiner Fubara for the opportunity to discuss the present case in the telephone interview on May 20, 2009. During the interview, the Examiner objected to the amendment to the specification in the Amendment and Response filed on March 16, 2009. The Examiner also objected to the term "derivatives" in claims 6 and 15. These objections are addressed in more detail below. The undersigned and the Examiner discussed in detail the differences between the claimed compositions and the prior art cited by the Examiner, particularly the limitation that the claimed poly(ester anhydride) have random ester bonds in the polymer backbone. The undersigned and the Examiner agreed that the claims are novel and non-obvious over the prior art.

In the Specification

The Examiner alleges that the recitation in claims 8 and 22 that the concentration of ricinoleic acid is at least 90% lacks antecedent support in the disclosure. Applicant respectfully disagrees. However, in order to facilitate allowance, the specification has been amended to describe this embodiment as requested by the Examiner. Support for the amendment is found at least in claim 8, as originally filed.

In the Claims

It is the undersigned's position that the pending claims are novel and non-obvious over the prior art. However, in order to facilitate allowance of the application, claim 1 has been amended to recite that the poly(ester anhydride) comprises anhydride monomers, oligomers, polymers, or combinations thereof, separated by the random ester bonds. Support for the

amendment is found at least in Figure 1 and page 13, lines 14-19. Applicant reserves the right to file one or more continuation applications with claims of a different or broader scope.

Claims 6 and 7 have been amended to correct typographical and grammatical errors. New claims 25 and 26 have been added. Support for new claims 25 and 26 are found at least at page 13, lines 21-24.

In the event this amendment and response does not overcome the Examiner's objections, the undersigned requests a telephonic interview with Examiner Fubara and her supervisor, SPE Hartley.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 6, 7, and 15-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Legal Standard

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). See also *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001) (unpublished). See also *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004) ("The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct

principles....Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite.").

Accordingly, a claim term that is not used or defined in the specification is not indefinite if the meaning of the claim term is discernible. *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004) (holding that the disputed claim term "surrender value protected investment credits" which was not defined or used in the specification was discernible and hence not indefinite because "the components of the term have well recognized meanings, which allow the reader to infer the meaning of the entire phrase with reasonable confidence").

Analysis

The Examiner alleges that claims 6 and 15 are indefinite because the boundaries of the term "ester derivatives" are not clearly defined. Claim 15 has been amended to delete the phrase "a derivative thereof". Therefore, the Examiner's rejection is moot with respect to claim 15.

Claim 6 depends from claim 1 and specifies that the poly(ester-anhydride) comprises one or more monomers derived from, among others, non-linear fatty acid-ester derivatives of ricinoleic acid. The specification discloses examples of non-linear fatty acid-ester derivatives of ricinoleic acid, such as alkyl O-esters and carbonates of ricinoleic acid and oligo(hydroalkanoic acid)-O-esters and carbonates of ricinoleic acid (page 14, lines 10-13); hydroxyl-acid terminated oligomers containing a ricinoleic acid terminal, such as poly(lactic acid)-terminated oligomers containing a ricinoleic acid terminal (page 14, lines 24-28); ricinoleic acid methyl ester (page 20, Example 1, Method 1); and ricinoleic acid stearyl ester, myristoyl ester, lauryl ester, octanoyl

ester, and ricinoleic acid-oligo lactide ester (pages 23-26, Example 2). One of ordinary skill in the art would understand the term "non-linear fatty acid-ester derivatives of ricinoleic acid", particularly when read in light of the specification. Accordingly, claim 6 is definite. However, without making any admissions and solely for the purpose of facilitating allowance, claims 6 and 15 have been amended to delete the term "derivative" and to recite the specific derivatives that are disclosed in the application as originally filed. Support for the amendment is found at least at page 14, lines 10-13 and lines 24-28; page 20, Example 1, Method 1); and pages 23-26, Example 2.

Rejection Under 35 U.S.C. § 102/§ 103

Claims 15-21 and 24 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,473,103 to Domb *et al.* ("Domb"). Claims 1 and 8 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,756,652 to Storey *et al.* ("Storey"). Claims 1-8 and 10 were rejected under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over Teomim *et al., J. Biomed. Mat. Res.*, Vol. 45, Issue 3, pp. 258-27 (1999) ("Teomim") or Domb *et al., Acta. Polym.,* Vol. 49, Issue 10-11, pp. 526-533 (1988) ("Domb 2"). Applicants respectfully traverse this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 US 947

(1987); *Scripps Clinic & Research Found v. Genentech Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in Scripps, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in Scripps, Id.:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986).

The Claimed Compositions

The claims are drawn to a drug delivery composition comprising a biodegradable, aliphatic poly(ester-anhydride) copolymer comprising random ester bonds along the polymer chain and a biologically active agent, wherein the poly(ester anhydride) comprises anhydride monomers, oligomers, polymers or combinations thereof, separated by the random ester bonds.

Analysis

Domb

Domb describes monomeric diacid derivatives that contain at least two fatty acids coupled by a hydrolytically or enzymatically degradable bond (abstract). Contrary to the Examiner's assertion, the polymers in Figure 2 are polyanhydrides, not poly(ester anhydrides) as required by claims 15-21 and 24 (*see* the legend in Figure 1). The polyanhydrides in Domb are prepared by polymerizing ricinoleic acid maleate (or other diacid monomer prepared by esterifying ricinoleic acid with a cyclic anhydride) with a diol or diacid to form polyanhydrides **or** polyesters (col. 4, lines 35-37 and col. 8, line 52 to col. 9, line 2). These polymers are polyanhydrides, not poly(ester anhydrides) having random ester bonds along the polymer chain as required by the claims. While the ricinoleic acid monomer does have an ester bond, it is within the monomer itself, formed by the reaction of the hydroxyl group of ricinoleic acid with the cyclic anhydride. It is not a random ester bond as required by the claims. Domb does not disclose each and every element of claims 15-21 and 24. Accordingly, claims 15-21 and 24 are novel over Domb.

Storey

Storey describes biodegradable poly(ester anhydrides) (abstract). The poly(ester anhydrides) of Storey are prepared by reacting a carboxy-terminated polyester, PE-COOH, or bis-carboxy-terminated polyester, HOOC-PE-COOH, with diphenylchlorophosphate to form a poly(ester anhydride) with a single anhydride linkage (*see* Figures 1C and 2C) or multiple anhydride linkages, respectively (col. 3, lines 57-65). However, in these materials, it is the anhydride linkage that is random, not the ester bond. Therefore, these polymers are structurally different from the claimed poly(ester anhydrides). Accordingly, claims 1 and 8 are novel over Storey.

The Examiner alleges that Storey does not exclude the ester moiety from being random so that randomness of the ester bond would be inherent. This is not the standard for inherency.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

The Examiner alleges that random ester bonds are inherent in the polymers described in Storey. However, the Examiner has provided no basis in fact and/or technical reasoning to reasonably support such an allegation as required under the doctrine of inherency. In fact, as discussed above, it is the anhydride linkage that is random in Storey's polymers, not an ester bond as required by the claims.

The Examiner also alleges that in response to Applicant's arguments that the ester bonds in the polymers in Figure 1 and 6 are at regular intervals, applicant has not pointed to applicant's polyester blocks having random ester bonds. Again, this is not the correct legal standard for inherency. Under the doctrine of inherency, the Examiner must provide a basis in fact and/or technical reasoning showing that random ester bonds are necessarily present in the polymers in Storey, not that the claimed compositions contain the inherent feature. The Examiner has provided no such factual basis and/or technical reasoning to support her allegation. However, as discussed above, applicant has shown that the ester bonds are random, for example, in Figure 1 of the application as originally filed.

Teomim

Teomim describes polyanhydrides synthesized from ricinoleic acid half-esters with maleic and succinic anhydrides (abstract). The polymers described in Teomim are polyanhydride copolymers that are formed from the melt condensation of diacids and contain only anhydride bonds between the monomer units. These are the same polymers described in Domb 1, prepared from the same starting materials in the same manner. While there are ester bonds within the monomer units (between the malic and succinate group and the hydroxyl group

of ricinoleic acid), there are no random ester bonds between monomers, oligomers, or polymers in the polymer backbone as required by claims 1-8 and 10. Teomim does not disclose or suggest poly(ester-anhydrides), let alone poly(ester-anhydrides) copolymers containing random ester bonds as required by independent claim 1 and the claims dependent thereon. Accordingly, claims 1-8 and 10 are novel and non-obvious over Teomim.

Further, one of ordinary skill in the art would not be motivated to modify the polyanhydrides of Teomim to arrive at the claimed compositions. The claimed compositions contain a poly(ester-anhydride) containing random ester bonds in the polymer backbone. The polymers are typically liquids at room temperature (page 7, lines 27-30) and thus can be administered by injection. The polymers release incorporated active agents over several weeks, which is longer than solid polymers prepared from the same monomers (page 7, lines 27-30). The slower release is due to the fact that when the polymer are placed in an aqueous medium (e.g., buffer solution, or tissue or biological mediums), the viscosity of the polymer increases (page 7, line 30 to page 8, line 3). This increase in viscosity results in a semisolid compact implant that keeps it integrity while slowly degrading and releasing incorporated drug (page 8, lines 3-6). These polymers also exhibited improved solubility compared to polyanhydrides (page 31, line 17 to page 32, line 2). The slower release of incorporated active agents and improved stability could not have been predicted from the polyanhydrides described in Teomim. Accordingly, claims 1, 8, and 9 are not obvious over Teomim.

Domb 2

Domb 2 describes biopolymers for use as drug carriers and bioactive macromolecules (abstract). Domb 2 discloses that polyanhydrides synthesized from non-linear hydrophobic fatty acid esters, based on ricinoleic acid, maleic acid, and sebacic acid (page 526, 2nd column, 4th paragraph, lines 8-11). These polymers are polyanhydrides (i.e., contain only anhydride bonds between monomer units), not poly(ester-anhydrides) as required by the claims.

Domb 2 also describes block copolyester-anhydrides (page 530, 1st col., 2nd paragraph). Domb 2 describes ABA-type block copolymers of poly(propylene fumarate) (PPF) and lactide (page 530, 1st col., 3rd paragraph). The polymers are represented by Structure 4. As shown in Structure 4, the bonds between monomers are anhydride bonds. Structure 4 does not show anhydride monomers, oligomers, polymers, or combinations thereof separated by random ester bonds as required by the claims. The only ester bonds in Structure 4 are within the PPF monomer unit. Domb 2 does not disclose each and every element of the claims. Accordingly, claims 1-8 and 10 are novel over Domb 2.

Further, one of ordinary skill in the art would not be motivated to modify the block copolyester-polyanhydrides of Domb 2 to arrive at the claimed composition. The Examiner admits that Domb 2 is silent regarding random ester bonds. However, the Examiner alleges that since Domb 2 prepares the polymers with the same reactants in the same manner as the applicants, the random ester bonds are inherent. Applicants respectfully disagree. As discussed above, the copolyester-polyanhydrides described in Domb 2 are block copolymers, wherein the ester bonds are between the monomer units in the ester block, not between anhydride blocks as

in the claimed compositions. The ABA block copolymers described in Domb 2 are prepared by ring opening polymerization of lactide using stannous octoate and PPF-diol as initiator (page 530, 1st col., 3rd paragraph). The ABA block copolymers described in Domb 2 are structurally different from the copolymers in the claimed composition. Alternatively, the Examiner alleges that the randomness of the ester bonds within the polymer would be obvious because the preparation method of Domb 2 does not exclude random ester bonds. Applicants respectfully disagree. As discussed above, the method of synthesis in Domb 2 clearly excludes random ester bonds. Accordingly, claims 1, 8, and 9 are not obvious over Domb 2.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 3, 9, and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Storey, in view of U.S. Patent No. 5,648,096 to Gander *et al.* ("Gander") or U.S. Patent No. 5,626,862 to Brem *et al.* ("Brem"). Claims 1 and 8 rejected under 35 U.S.C. § 103(a) as being unpatentable over Teomim or Domb 2. Claims 15, 19, and 21-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Domb in view of O'Hagan, *Adv. Drug Del. Rev.*, 1 Dec., pp. 305-320 (1998) ("O'Hagan"). Applicants respectfully traverse this rejection.

Legal Standard

"The proper analysis under § 103, was recently reviewed by the U.S. Supreme Court in KSR International, Inc. v. Teleflex, Inc, 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289. In KSR, the Court stated:

"If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, §103 likely bars its patentability. Moreover, if a technique

has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to the interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences, and creative steps a person of ordinary skill in the art would employ."

Where there is structural similarity between a chemical compound and prior art compounds, the court notes that, "obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound." Slip Op. at 4 (citing *Takede Chem. Indus. v. Alpha Farm Pty., Ltd.*, supra, 492 F.3d at 1356). The Federal Circuit notes that, under KSR, what must be demonstrated is the

possession of a sufficiently close relationship between the claimed and the prior art compound to create an expectation, in light of the entirety of the prior art, that the new compound will have similar properties to the old. (citing *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, supra, which relied upon *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). Thus, even though the prior art compound and the patented compound were virtually identical except for a substitution at a particular position on a pyridine ring, because expert testimony showed (1) there were significant differences between compounds that achieved anti-ulcer action and compounds that inhibited gastric acid and (2) the prior art compound provided a special path to achieve certain results, the prior art did not make the claimed compound obvious. There was no discernable reason for a skilled artisan to start with this "lead" prior art compound but then to modify it in a way that would eliminate an element of it to which this advantageous property was ascribed. Thus, it would not have been obvious to try certain substitutions in the chemical structure of the prior art compound to achieve the results found in the patented compound.

Even where the prior art suggests or motivates an inventor to develop the composition or process at issue, the Federal Circuit continues to recognize that there is a critical question under 35 U.S.C. § 103 as to whether the combined teachings of the prior art "would have given rise to a reasonable expectation of success" in achieving what is claimed. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007), petition for cert. filed, 76 U.S.L.W. 3393 (U.S. Jan. 2, 2008) (No. 07-888).

Storey in view of Gander or Brem

Storey is discussed above. Storey does not disclose or suggest a poly(ester-anhydride) containing random ester bonds along the polymer backbone as required by independent claim 1 and the claims dependent thereon.

Gander and Brem disclose microimplants, such as microparticles, microspheres, and microcapsules can be used to encapsulate and deliver drugs. Gander and Brem, alone or in combination, do not cure the deficiencies of Storey. Accordingly, claims 1-10 and 15-24 are not obvious over Storey in view of Gander or Brem.

Domb 2 or Teomim

The obviousness rejections over Domb2 and Teomim are discussed above.

Domb 1 in view of O'Hagan

Domb 1 is discussed above. Domb does not disclose or suggest poly(ester-anhydrides) having random ester bonds along the polymer backbone. O'Hagan describes microparticles and polymers for the mucosal delivery of vaccines (abstract). O'Hagan does not cure the deficiencies of Domb. Accordingly, claims 15, 19, and 21-23 are not obvious over Domb in view of O'Hagan.

Allowance of claims 1-10 and 15-24, as amended, and new claims 25-27, is respectfully solicited.

Respectfully submitted,

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